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Original article

Increased extent of myocardial fibrosis in genotyped hypertrophic cardiomyopathy with ventricular tachyarrhythmias

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ABSTRACT

Background: Occurrence of malignant ventricular tachyarrhythmias such as ventricular tachycardia and fibrillation (VT/VF) in hypertrophic cardiomyopathy (HCM) can be related to the extent of myocardial fibrosis. Although late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) imaging has been used to detect myocardial fibrosis, few data exist regarding relationships between CMR-determined myocardial fibrosis and VT/VF in genotyped HCM populations.
Objective: We retrospectively investigated whether the extent of LGE can be increased in HCM patients with VT/VF compared to those without VT/VF in the genotyped HCM population.
Methods and results: We studied 35 HCM patients harboring sarcomere gene mutations (*TNNI3* = 22, *MYBPC3* = 12, *MYH7* = 1) who underwent both CMR imaging and 24-h ambulatory electrocardiographic monitoring. VT/VF were identified in 6 patients (2 men, mean age 55.0 years). The extent of LGE was significantly increased in patients with VT/VF ($n = 6$) compared with those without VT/VF ($n = 29$) ($18.6 \pm 14.4\%$ vs. $8.3 \pm 11.4\%$, $p = 0.04$), although the LGE extent was not an independent predictor for the occurrence of VT/VF. Applying a cut-off point $\geq 3.25\%$, episodes of VT/VF were identified with a sensitivity of 100%, specificity of 51.7%, positive predictive value of 30%, negative predictive value of 100%, and the area under the curve of 0.767 (95% confidence interval: 0.590–0.944).
Conclusion: These results demonstrate that myocardial fibrosis determined by CMR imaging may be increased in genotyped HCM patients with episodes of VT/VF. A further prospective study will be needed to clarify the association between the LGE extent and arrhythmic events in HCM patients harboring sarcomere gene mutations.

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disease, and mutations in 11 or more genes encoding proteins of the cardiac sarcomere (>1400 variants) are associated with HCM [1,2]. Although the overall prognosis of HCM may not be unfavorable, hereditary HCM with sarcomere gene mutations may be associated with increased cardiovascular events [3,4]. Moreover, in some cases sudden death associated with malignant ventricular tachyarrhythmias such as ventricular tachycardia and fibrillation (VT/VF) may occur, particularly in young adults [5–7]. Under these conditions, the occurrence of these arrhythmias may be related to the extent of myocardial fibrosis [8]. However, few clinical data exist regarding the relationship between myocardial fibrosis and occurrence of ventricular tachyarrhythmia particularly in HCM with sarcomere gene mutations.

Evaluation of late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) imaging enables us to detect myocardial fibrosis and to examine whether LGE is associated with

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the occurrence of VT/VF in HCM [9,10]. In the present study, using CMR imaging we investigated the correlation between the extent of myocardial fibrosis and VT/VF in HCM patients in whom sarcomere gene mutations were identified.

Methods

Study patients

The diagnosis of HCM was based on the guidelines of the American College of Cardiology Foundation/European Society of Cardiology [11]. Patients with coronary artery disease, intrinsic valve dysfunction, and idiopathic pulmonary artery hypertension were excluded from the study. We screened for mutations in sarcomere genes in 488 unrelated HCM probands (377 men) who were diagnosed at Kanazawa University Hospital and affiliated hospitals [12]. Sarcomere gene mutations were identified in 69 of the 488 probands. Family studies of these 69 probands revealed an additional 88 mutation carriers; thus in total 157 mutation carriers were identified. Of these, 35 HCM patients harboring sarcomere genes' mutations who underwent both CMR and 24-h Holter electrocardiogram (ECG) monitoring were included in this study. All clinical evaluations for the 35 patients were performed from 2005 to 2009 at the Kanazawa University Hospital, and data were retrospectively collected. Informed consent for genetic analysis and use of clinical data for research was obtained from all subjects or their guardians. The study was approved by the Bioethical Committee on Medical Research, School of Medicine, Kanazawa University.

Genetic analysis

Mutations in translated exons of the 8 common sarcomere genes were screened: cardiac myosin binding protein C (*MYBPC3*), cardiac myosin heavy chain (*MYH7*), cardiac regulatory and essential myosin light chains (*MYL2* and *MYL3*), cardiac troponin I (*TNNI3*), cardiac troponin T (*TNNT2*), cardiac tropomyosin (*TPM1*), and cardiac actin (*ACTC1*). Mutations were screened using the polymerase chain reaction (PCR) and the single-strand conformational polymorphism (SSCP) technique or high resolution melting (HRM) analysis (LightScanner System, Idaho Technology, Salt Lake City, UT, USA). For the abnormal SSCP or HRM patterns, PCR products were directly sequenced to identify mutations [4].

Clinical evaluations

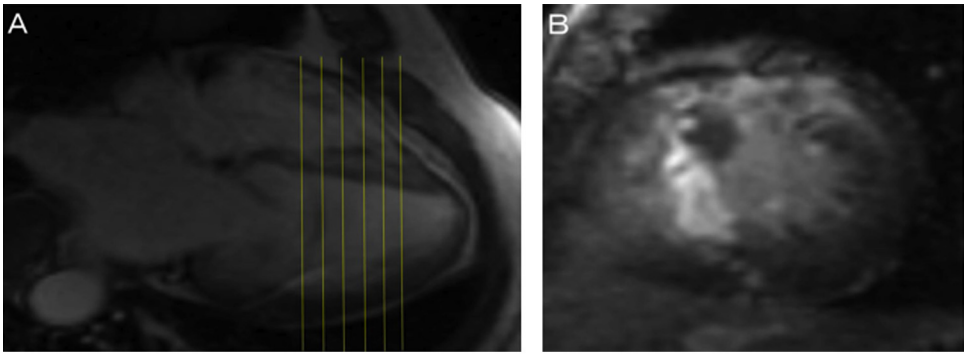
The 35 HCM patients underwent 12-lead standard ECG, 24-h ambulatory ECG monitoring, echocardiography, and CMR. All clinical evaluations were performed from 2005 to 2009 at the Kanazawa University Hospital, and data were retrospectively collected.

Standard M-mode and 2-dimensional echocardiographic studies were performed by sonographers with knowledge of HCM diagnosis but without knowledge of CMR parameters to avoid potential measurement bias. Measured parameters included thicknesses of the interventricular septum and left ventricular (LV) posterior wall at the level of the tips of the mitral valve leaflets. Fractional shortening was calculated as (end-diastolic dimension–end-systolic dimension)/end-diastolic dimension. LV ejection fraction was calculated with Simpson's method [13]. Impaired systolic LV function was defined when LV ejection fraction was $<50\%$ [14].

CMR images were acquired by using a 1.5-T Signa MR unit (Echo speed CVi) with a cardiac coil (GE Medical Systems, Milwaukee, WI, USA). Fast spoiled gradient recalled acquisition cines were acquired during 8-second breath-holds (the echo time/repetition time 1.3/5.0 ms, flip angle 30°) in long-axis planes and sequential 8-mm short-axis slices (2 mm gap between slices) from the apex to the atrioventricular ring. Intravenous gadolinium with diethylenetriamine pentaacetic acid was given (0.2 mmol/kg) and contrast-enhanced images were acquired after 10–15 min in 8–10 identical short-axis planes and 4-chamber view planes by using an inversion-recovery segmented gradient echo. Inversion times were adjusted to null normal myocardium (230–350 ms) with voxel sizes of 2.0 mm $\times$ 1.6 mm $\times$ 8.0 mm [15]. Hyperenhanced areas were calculated by manual planimetry in all short-axis slices and the total areas of hyperenhancement are expressed as a percentage of total myocardium (Fig. 1) [16,17]. All imaging studies were analyzed separately by two observers without knowledge of clinical findings. In patients with VT/VF, the areas of LGE were indicated in the American Heart Association/American College of Cardiology 17-segment model nomenclature [18].

Evaluation of arrhythmic events

Arrhythmic events were defined as sudden cardiac death, non-sustained VT, sustained VT, and VF. Documentation of these events was based on records of VT/VF on an automated external defibrillator, 24-h Holter ECG, continuous ECG monitoring, the use of an implantable defibrillator, or the occurrence of sudden



$$\text{The extent of LGE (\%)} = \frac{\text{The areas of total hyperenhancement (cm}^2\text{)}}{\text{The areas of total myocardium (cm}^2\text{)}}$$

Fig. 1. Methods for evaluation of the extent of late gadolinium enhancement (LGE). (A) Areas of LGE were measured in short-axis slices. (B) The total areas of LGE were measured by manual planimetry and were expressed as a percentage of total myocardium.